REMARKS

Applicant requests reconsideration of the application in view of the foregoing amendments and the discussion that follows. The status of the claims as of this response is as follows: Claims 1-36 are pending, Claims 7, 8, and 10-24 have been withdrawn and Claims 9 and 25-36 have been canceled herein. Applicant reserves the right to file divisional applications to the separately patentable subject matter thereof. Claims 1- 4 have been amended herein and Claims 37-46 have been added.

The Amendments

The Specification was amended to correct obvious typographical errors and to amend the title as suggested in the Office Action.

Claim 1 was amended to recite "bound to" in place of "associated with" in all occurrences. Support therefor is in the Specification, for example, the paragraph bridging pages 52 and 53. Claim 1 was also amended to recite "proximity" in place of "association." Support therefor is in the Specification, for example, the paragraph bridging pages 52 and 53. Claim 1 was also amended to recite that the excitation of the sensitizer causes the formation of reactive oxygen, which cleaves the cleavable linker and releases detectable substrate from the support. Claim 1 was also amended to incorporate the elements of Claim 9.

Claim 2 was amended to correct typographical errors and to recite that the proximity of the first and second specific binding pair members to one another results from the binding of the first and second specific binding pair members to the analyte. The latter amendment was necessitated to provide proper reference back to the base claim, i.e., Claim 1.

Claim 3 was amended to recite that the step of detecting the released detectable substrate is carried out by a detection method employing avidin bound to a member of a signal producing system or anti-digoxigenin antibodies bound to a member of a signal producing system or both. Support therefor is in the Specification, for example, paragraph bridging pages 16 and 17 and Example 5.

Claim 4 now recites that the olefin or the aromatic compound is cleaved by reactive oxygen. Support therefor is in the Specification, for example, page 19, lines 19-23, and original Claims 2 and 4.

Claims 37-43 were added.

Claim 37 is directed to the method of Claim 3 wherein the signal producing system involves generation of luminescence. Support therefor is in the Specification, for example, page 1, line 13, and original Claim 3.

Claim 38 is directed to the method of Claim 37 wherein avidin is bound to a photosensitizer and anti-digoxigenin antibodies are bound to a chemiluminescer molecule. Support therefor is in the Specification, for example, paragraph bridging pages 16 and 17 and Example 5.

Claim 39 is directed to the method of Claim 3 wherein the signal producing system involves generation of fluorescence. Support therefor is in the Specification, for example, page 1, line 13, and original Claim 3.

Claim 40 is directed to the method of Claim 39 wherein avidin is bound to a photosensitizer and anti-digoxigenin antibodies are bound to a photoactive indicator precursor. Support therefor is in the Specification, for example, page 21, lines 10-15.

Claim 41 is directed to the method of Claim 3 wherein the signal producing system involves enzyme activity. Support therefor is in the Specification, for example, page 2, lines 26-27, and original Claim 3.

Claim 42 is directed to the method of Claim 3 wherein the signal producing system involves radioactivity. Support therefor is in the Specification, for example, page 2, lines 26-27, and original Claim 3.

Claim 43 is directed to the method of Claim 3 wherein the signal producing system involves fluorescence energy transfer. Support therefor is in the Specification, for example, page 2, lines 20-21, and original Claim 3.

Claim 44 is directed to a method for amplifying a signal from a binding assay wherein the method comprises providing a reaction mixture comprising in combination a medium suspected of containing an analyte; a first specific binding pair member bound to a support; a second specific binding pair member bound to a sensitizer capable in its excited state of generating a reactive oxygen species, wherein the proximity of first

specific binding pair member with the second specific binding pair member is modulated by the presence of the analyte; and a detectable substrate bound to the support through a reactive oxygen cleavable linker wherein the detectable substrate comprises digoxigenin-linked biotin; incubating the reaction mixture; exciting the sensitizer, the excitation of the sensitizer causing the formation of reactive oxygen, which cleaves the cleavable linker and releases detectable substrate from the support; and detecting the released detectable substrate. Support therefor is in the Specification, for example, original Claims 1 and 3.

Claim 45 is dependent from Claim 44 and recites that the proximity of the first and second specific binding pair members to one another results from the binding of the first and second specific binding pair members to the analyte; the sensitizer is a photosensitizer; the reactive oxygen species is singlet oxygen; and the excitation step comprises irradiation of the photosensitizer with light. Support therefor is in the Specification, for example, original Claim 2.

Claim 46 is dependent from Claim 44 and recites that the step of detecting the released detectable substrate is carried out by a detection method employing avidin bound to a member of a signal producing system or anti-digoxigenin antibodies bound to a member of a signal producing system or both. Support therefor is in the Specification, for example, paragraph bridging pages 16 and 17 and Example 5.

Restriction Requirement and Election of Species

Applicant acknowledges the indication in the Office Action that Group II was modified to include both Claims 25 and 26 and that Group III is eliminated. Applicant further acknowledges that the restriction requirement has involved a determination at least implicitly that the inventions of the various groups are separately patentable over one other and that each invention of the various groups must be novel and unobvious over the inventions of the other groups.

Applicant again acknowledges the indication in the previous Election of Species that, upon the allowance of a generic claim, Applicant will be entitled to consideration of claims to additional species that are written in dependent form or otherwise include all the limitations of an allowed generic claim.

Specification

This response includes a new title thereby obviating the objection regarding the previous title.

Rejection under 35 U.S.C. 112

Claims 1-6 and 9 were rejected under the second paragraph of the above code section as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In particular, the Office alleges that the term "substrate" is indefinite. Applicant respectfully traverses this ground of rejection. As can be seen from Applicant's Specification, page 9, lines 5-22, substrate is attached by a cleavable linker, which, when cleaved, releases multiple substrates as multiple products. The released substrate is also referred to in the Specification as the product. The language in the Specification, page 4, lines 24-26, does not render the term "substrate" indefinite. As can be seen from the Specification, there is substrate that is bound by means of a cleavable linker to a support. Generation of a reactive oxygen species cleaves the linker releasing a portion or all of the substrate. This released substrate (or product) is detected. In some instances the released substrate can be detected without separation from the substrate bound to the support. In other instances, the released substrate must be separated from the bound substrate. If the bound substrate is incapable of binding during the detection process, then no separation is required. If not, then the released substrate is separated from the bound substrate.

It is submitted that the deletion of the term "ligand" from Claim 1 obviates the rejection of Claim 1 for recitation of such term.

It is submitted that the deletion of the phrase "associated with" from Claim 1 obviates the rejection of Claim 1 for recitation of such term.

Claim 1 was amended to recite that the excitation of the sensitizer causes the formation of reactive oxygen, which cleaves the cleavable linker and releases detectable substrate from the support. Such amendment obviates the perceived indefiniteness with respect to whether or not the cleavable linker is cleaved.

Claim 1 now recites that the excitation of the sensitizer generates reactive oxygen, which cleaves the cleavable linker. This amendment obviates the rejection of Claim 1 under the second paragraph of the above code section as being incomplete for omitting essential steps.

Applicant submits that the amendments to Claim 2 obviate the rejection of Claim 2 under the second paragraph of the above code section.

Applicant submits that the amendments to Claim 3 obviate the rejection of Claim 3 under the second paragraph of the above code section.

Applicant respectfully traverses the rejection of Claim 5 as indefinite for the recitation of dioxenes, thioxenes and oxazines because, alleges the Office Action, it is not clear how cleavage of the linkers results in release of detectable substrate. Applicant's Specification, paragraph bridging pages 37 and 38, provides examples of reactions of the above types of groups with reactive oxygen leading to the release of moieties attached by means of such groups. Furthermore, an oxazine may function as a cleavable linker with appropriate substituents for promoting cleavage by reactive oxygen as indicated in the specification. Oxazines may also function as photosensitizers where they do not contain substituents that promote cleavage by reactive oxygen.

The rejection of Claim 6 is traversed for reasons similar to those above in the traversal of the rejection of Claim 5.

Claim 9 (now incorporated into Claim 1) was rejected for the recitation of "or indirectly" as indefinite because it is not clear what type of spatial relationship is created by "indirectly" binding or which entities are included in the binding interaction. Furthermore, continues the Office Action, a person of ordinary skill in the art cannot ascertain the standard or degree of indirectness required by "indirectly." The Specification, page 54, lines 6-10, defines the phrase "capable of binding directly or indirectly." Accordingly, one skilled in the art would have an understanding of the meaning of the phrase.

Rejection under 35 U.S.C. 102

Claims 1-6 and 9 were rejected under paragraph (e) of the above code

section as being anticipated by Singh, *et al.* (U.S. Patent No. 6,770,439) (Singh). The reference discloses probe sets for the multiplexed detection of the binding of, or interaction between, one or more ligands and target antiligands. Detection involves the release of identifying tags as a consequence of target recognition. The probe sets include electrophoretic tag probes or e-tag probes, comprising a detection region and a mobility-defining region called the mobility modifier, both linked to a target-binding moiety. Target antiligands are contacted with a set of e-tag probes and the contacted antiligands are treated with a selected cleaving agent resulting in a mixture of e-tag reporters and uncleaved and/or partially cleaved e-tag probes. The mixture is exposed to a capture agent effective to bind to uncleaved or partially cleaved e-tag probes, followed by electrophoretic separation. In a multiplexed assay, different released e-tag reporters may be separated and detected providing for target identification.

Singh does not disclose or suggest the method of Claim 1. Among others, there is no disclosure or suggestion in Singh of a method as recited wherein the step of detecting the released detectable substrate comprises the steps of (a) separating the released detectable substrate from the detectable substrate associated with the support; (b) adding to the separated released detectable substrate, a third specific binding pair member capable of binding directly or indirectly to the released detectable substrate; (c) allowing the third specific binding pair member to bind to the released detectable substrate; and (d) detecting the bound third specific binding pair member.

The Office Action argues that Singh teaches a method for amplifying a signal from a binding assay wherein the step of detecting the released detectable substrate comprises the steps of: separating the released detectable substrate from the detectable substrate associated with the support, adding to the separated released detectable substrate a third specific binding pair member capable of binding directly to the released detectable substrate, allowing the third specific binding pair member to bind, and detecting the bound third specific binding pair member. In support of this contention, the Office Action refers to col. 29, lines 6-8, and Fig. 3B of the reference).

At col. 29, lines 6-8, and Fig. 3B, the patentee discusses the use of a capture ligand. As used by Singh, the term "capture ligand" refers to a group that is typically

included within the target binding moiety or portion of an e-tag probe and is capable of binding specifically to a "capture agent" or receptor. The interaction between such a capture ligand and the corresponding capture agent may be used to separate uncleaved e-tag probes from released e-tag reporters (col. 17, lines 12-18). This disclosure has no informative value with regard to the presently claimed method. In particular, Claim 1 recites "a third specific binding pair member capable of binding directly or indirectly to the released detectable substrate" and "detecting the bound third specific binding pair member." In Singh the capture agent binds to the capture ligand of the uncleaved e-tag probes. See also Fig. 3B. Furthermore, there is no disclosure or suggestion in Singh of detecting the bound third specific binding pair member.

The Office Action rejected Claim 3 under the above code section and alleges that Singh teaches a method for amplifying a signal from a binding assay wherein the substrate comprises digoxigenin-linked biotin (see col. 29, lines 6-8, "biotin and strept/avidin... digoxin or derivative thereof and antidigoxin), and detection comprises avidin and anti-digoxigenin antibodies (see col. 29, lines 6-8, "biotin and strept/avidin... digoxin or derivative thereof and antidigoxin).

However, as explained above, at col. 29, lines 6-8, and Fig. 3B, the patentee is discussing the use of a capture ligand. As used by Singh, the term "capture ligand" refers to a group that is typically included within the target binding moiety or portion of an e-tag probe and is capable of binding specifically to a "capture agent" or receptor. The interaction between such a capture ligand and the corresponding capture agent may be used to separate uncleaved e-tag probes from released e-tag reporters (col. 17, lines 12-18). This disclosure has no informative value with regard to the presently claimed method. In particular, Claim 3 recites that the substrate comprises digoxigenin-linked biotin and the step of detecting the released detectable substrate is carried out by a detection method employing avidin bound to a member of a signal producing system or anti-digoxigenin antibodies bound to a member of a signal producing system or both. In Singh the capture agent binds to the capture ligand of the uncleaved e-tag probes. See also Fig. 3B.

Singh does not disclose or suggest the methods of new Claims 37-46 for reasons similar to those presented above.

Conclusion

Applicant has demonstrated that Claims 1-6 and 37-46 satisfy the requirements of 35 U.S.C. 112 and 102. Allowance of the above-identified patent application, it is submitted, is in order.

Respectfully submitted,

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